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Nicotinamide: A cardioprotective form of Vitamin B3

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Abstract

Nicotinamide, a form of vitamin B3, has emerged as a potential cardioprotective agent against ischemia-reperfusion (I/R) injury, a critical factor in the pathogenesis of myocardial infarction, heart failure, and other cardiovascular diseases. This compound plays a significant role in energy metabolism, DNA repair, and cell survival by participating in the biosynthesis of NAD+, a coenzyme essential in redox reactions.

The underlying mechanism of cardioprotection afforded by nicotinamide involves enhancing NAD+ biosynthesis, which in turn regulates SUR2A to modulate ATP-sensitive K^+ (K_{ATP}) channels, influences sirtuin activity, and affects poly(ADP-ribose) polymerases (PARPs) activity to conserve NAD+ levels. Additionally, nicotinamide exhibits anti-inflammatory properties, regulates autophagy, and exerts antioxidant effects, collectively contributing to its potential to mitigate the impact of I/R injury on the myocardium.

Despite its wide range of therapeutic applications and safety profile, distinctions between nicotinamide and another form of vitamin B3 nicotinic acid (niacin) are crucial, especially regarding their effects on lipid profiles and vascular functions. Unlike niacin, nicotinamide does not affect lipid levels or pose a risk of increasing cardiovascular events, highlighting its safety for clinical use at recommended doses. However, so far, no clinical study of nicotinamide in the context of cardioprotection has been done. Randomized controlled trials are clearly needed to examine nicotinamide's possible role in clinical practice, define optimal dosing strategies, and understand its long-term effects. However, considering the history of nicotinamide use, this is a compound that could be quickly introduced in clinical practice for cardioprotection.

Key words: cardioprotection, nicotinamide

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Introduction

Cardioprotection is defined as the ability of the heart to withstand different types of metabolic stresses, including ischemia-reperfusion (I/R), which underlies acute myocardial infarction. I/R injury is characterized by a restricted blood supply to the cardiac muscle (ischemia), followed by the restitution of the blood flow (reperfusion). Paradoxically, reperfusion, occurring following ischemia, leads to exacerbation of cardiac muscle damage through different events, including oxidative stress, calcium overload, inflammation, and apoptosis. As I/R plays a crucial role in the pathogenesis of myocardial infarction, heart failure, and other cardiovascular diseases, the clinical significance of counteracting I/R injury is of the highest order (1).

In the quest for clinically effective cardioprotective strategies, the focus has been on pharmacological agents capable of protecting the myocardium from the deleterious effects of I/R injury. Nicotinamide, a form of vitamin B3 and a precursor of nicotinamide adenine dinucleotide (NAD+), has emerged as a potential compound of interest. Nicotinamide plays important roles in different metabolic processes, including energy metabolism, DNA repair, and cell survival, primarily through the biosynthesis of NAD+, which is an important coenzyme in redox reactions (2). In addition, nicotinamide has also been involved in modulating the activity of sirtuins and poly(ADP-ribose) polymerases (PARPs), enzymes that are part of cellular responses to metabolic stress, including those elicited by I/R injury (3).

The potential of nicotinamide as a cardioprotective agent lies in its metabolic functions, as well as in its ability to target key pathways involved in the pathophysiology of I/R injury and cardioprotective signaling. Through its effects on NAD+ biosynthesis, sirtuin activity, and PARP-mediated DNA repair, nicotinamide has shown promise in many preclinical studies (4).

Nicotinamide: an overview

Nicotinamide, also known as niacinamide, is a water-soluble form of vitamin B3 or niacin. It plays an important role in human health, primarily by serving as a precursor to nicotinamide adenine dinucleotide (NAD+), which is a coenzyme essential for various cellular processes. As opposed to niacin, nicotinamide does not cause vasodilation, known as "niacin flush" (5).

Chemically, nicotinamide is an amide derivative of nicotinic acid. It participates in redox reactions within the cell, which is crucial for the production of ATP and the maintenance of cellular energy balance. It is well established that NAD+, the coenzyme derived from nicotinamide, is essential for oxidative phosphorylation and glycolysis as it serves as an electron transporter in these energy-generating pathways. In addition to that, NAD+ is critical for DNA repair, gene expression regulation, and signaling pathways regulating cell survival (5).

Following the discovery that niacin deficiency causes dermatitis, diarrhea, dementia, and eventually death, nicotinamide has been extensively studied for its

therapeutic potential in various conditions, including skin disorders, type 1 diabetes, and neurodegenerative diseases. Nicotinamide is used in skin health, particularly for acne and aging-related conditions. In metabolic diseases, nicotinamide is used to enhance insulin sensitivity and support beta-cell function in the pancreas. It has been suggested that nicotinamide harbors neuroprotective properties, which could be exploited in the therapy of Alzheimer's disease and other neurodegenerative conditions (6-10).

In the context of cardiovascular health, nicotinamide plays a role that extends beyond the prevention of deficiency diseases. It is involved in NAD+ biosynthesis and sirtuin activation, both of which are events involved in cellular responses to stress, including those during ischemia. The cardioprotective potential of nicotinamide has been suggested and it seems to be rooted in its ability to modulate metabolic and signaling pathways critical for reducing I/R injury's impact on the myocardium (3-5).

Mechanisms of Cardioprotection by Nicotinamide

The mechanism of cardioprotection afforded by nicotinamide seems to be complex and multifaceted. It involves the modulation of cellular energy metabolism, promotion of DNA repair, anti-inflammatory effects, regulation of cell death pathways, and regulation of SUR2A expression (11).

NAD+ Biosynthesis

The basis of nicotinamide's cardioprotective effect is generally accepted to be its role in enhancing NAD+ biosynthesis. NAD+ is a crucial element in cellular energy metabolism, as it serves as a key cofactor for enzymes involved in oxidative phosphorylation and glycolysis. During I/R injury, NAD+ levels significantly decrease, leading to decreased ATP production and exacerbation of cellular damage. Nicotinamide supplementation increases NAD+ levels, which in turn facilitates ATP production and stabilizes cellular energy balance counteracting the detrimental effects of I/R injury on cardiac cells (6, 10).

Regulation of SUR2A

SUR2A is a regulatory subunit of sarcolemmal ATP-sensitive K^+ (K_{ATP}) channels. It has been shown that oral nicotinamide regulates the expression of SUR2A, which in turn regulates the level of fully-assembled K_{ATP} channels conferring cardioprotection by preventing Ca^{2+} influx and maintaining subsarcolemmal ATP levels by the activity of enzymes physically associating with the channel subunits (11-13; Fig. 1). It has been demonstrated that cardioprotection afforded by oral nicotinamide is abolished when sarcolemmal K_{ATP} channels are blocked (Fig. 1; 14, 15).

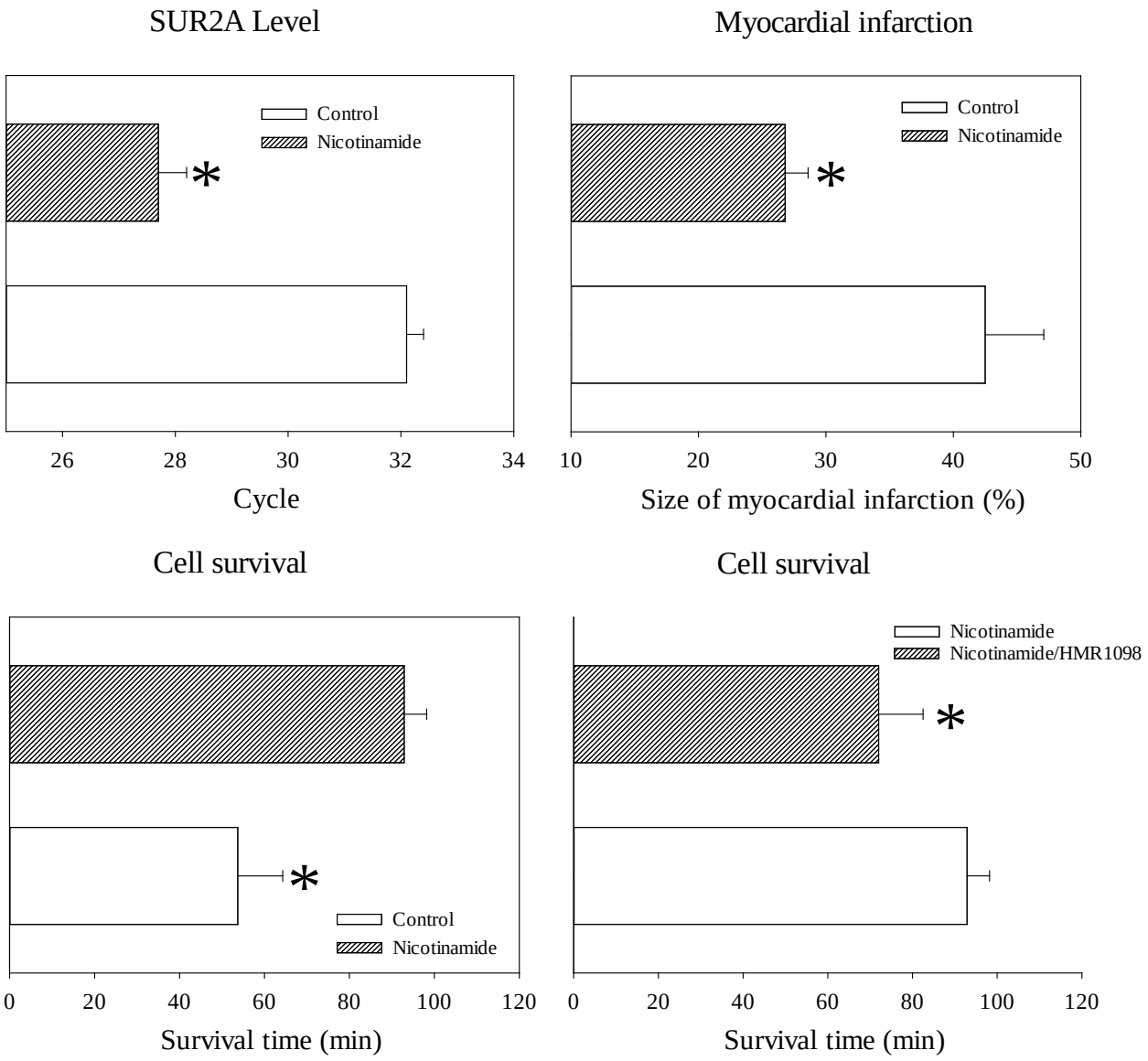

Figure 1. Regulation of SUR2A and cardioprotection afforded by nicotinamide. **Graphs depicting real-time RT-PCR cycling thresholds in hearts of mice on standard (control) and nicotinamide-rich (nicotinamide) diet (SUR2A levels). Size of myocardial infarction in whole heart model of ischemia-reperfusion (myocardial infarction) and the longevity of survival of beating cardiomyocytes exposed to hypoxia in the absence (cell survival left panel) and presence of K_{ATP} channel blocker HMR1098 (30 μM) (cell survival right panel) in mice on standard (control) and nicotinamide-rich (nicotinamide) diet. Each bar is mean ±SEM (n=6-10). *P<0.05. Graphs are made based on data published in reference 14, where corresponding methods are also described in detail.**

Slika 1. Regulacija SUR2A i kardioprotekcije koju pruža nikotinamid.
Grafikoni prikazuju broj ciklusa RT-PCR u realnom vremenu u srcima miševa na standardnoj (kontrolnoj) i nikotinamidom bogatoj (nikotinamid) ishrani (nivo SUR2A). Veličina infarkta miokarda na izolovanom srcu i dužina preživljavanja kardiomiocita izloženih hipoksiji u odsustvu (preživljavanje ćelija, levi panel) i prisustvu blokatora KATP kanala HMR1098 (30 μM) (preživljavanje ćelija, desni panel) kod miševa na standardnoj (kontrolnoj) i nikotinamidom bogatoj (nikotinamid) ishrani. Svaki stubić predstavlja srednju vrednost ±SEM (n=6-10). *P<0,05. Grafikoni su sačinjeni na osnovu podataka objavljenih u referenci 14, gde su odgovarajuće metode takođe detaljno opisane.

Modulation of Sirtuin Activity

It has been reported that sirtuins, a family of NAD+-dependent deacetylases, play important roles in regulating cellular stress responses. They are involved in DNA repair, apoptosis, and inflammation. It has been suggested that nicotinamide regulates sirtuin activity, especially SIRT1, which has been shown to result in cardioprotective outcomes. Nicotinamide activates SIRT1, leading to deacetylation of target proteins involved in antioxidant defense and mitochondrial function, which increases myocardial resistance to I/R injury (3, 4).

Effects on PARP Activity

Poly(ADP-ribose) polymerases (PARPs) are enzymes that are involved in DNA repair processes. It has been shown that PARP1 is activated in response to DNA damage to facilitate DNA repair. This process is NAD+-dependent and excessive PARP1 activation can deplete cellular NAD+ reserves, thereby impairing energy metabolism and promoting cell death. Nicotinamide inhibits PARP1 activity, which results in the conservation of NAD+ levels and the prevention of energy depletion occurring in I/R injury, thus protecting cardiomyocytes from damage (16, 17).

Impact on Inflammation and Apoptosis

I/R injury triggers an inflammatory response involving the activation of pro-inflammatory cytokines, and infiltration of inflammatory cells into the myocardium, which contributes to tissue damage. Nicotinamide regulates the NF-κB pathway, resulting in the reduced expression of pro-inflammatory cytokines and limiting inflammatory cell recruitment, which, taken together, induces a strong anti-inflammatory effect. Nicotinamide also regulates apoptosis regulatory proteins, including Bcl-2 and caspases, leading to an increase in cell survival and a decrease in apoptosis in the ischemic myocardium (18, 19).

Regulation of Autophagy

Autophagy is a process of cellular cleanup and recycling, which plays a dual role in I/R injury. More specifically, it can be either protective or detrimental depending on the context. Nicotinamide has been implicated in the regulation of autophagy in cardiac cells. It enhances the removal of damaged organelles and proteins while preventing excessive autophagic cell death, which helps to maintain cellular integrity and function during and after I/R (19, 21).

Antioxidant Effects

Oxidative stress is one of the major events in the I/R challenge, with the overproduction of reactive oxygen species (ROS), which leads to cellular damage. Nicotinamide possesses antioxidant effects, either directly by scavenging ROS or indirectly by upregulating the expression of antioxidant enzymes. The effect of reducing oxidative stress contributes to the preservation of myocardial tissue and function (22).

The proposed mechanisms of cardioprotection afforded by nicotinamide are summarized in Table I.

Table I Mechanism mediating cardioprotection afforded by nicotinamide

Tabela I Mehanizam koji posreduje u kardioprotekciji koju pruža nikotinamid

Mechanism	Description	References
NAD+ Biosynthesis	Enhances NAD+ levels, facilitating ATP production and stabilizing cellular energy balance, counteracting the detrimental effects of ischemia-reperfusion (I/R) injury on cardiac cells.	(6, 10)
Regulation of SUR2A	Regulates the expression of SUR2A, which in turn regulates the level of fully-assembled KATP channels, preventing Ca2+ influx and maintaining subsarcolemmal ATP levels. Cardioprotection is abolished when KATP channels are blocked.	(11-13, 14, 15)
Modulation of Sirtuin Activity	Activates SIRT1, leading to deacetylation of target proteins involved in antioxidant defense and mitochondrial function, increasing myocardial resistance to I/R injury.	(3, 4)
Effects on PARP Activity	Inhibits PARP1 activity, conserving NAD+ levels and preventing energy depletion, thus protecting cardiomyocytes from damage.	(16, 17)

Impact on Inflammation and Apoptosis	Regulates the NF-κB pathway, reducing pro-inflammatory cytokines and limiting inflammatory cell recruitment. Also regulates apoptosis regulatory proteins, increasing cell survival and decreasing apoptosis.	(18, 19)
Regulation of Autophagy	Enhances the removal of damaged organelles and proteins while preventing excessive autophagic cell death, maintaining cellular integrity and function during and after I/R.	(19, 21)
Antioxidant Effects	Possesses antioxidant effects by scavenging ROS or upregulating antioxidant enzymes, reducing oxidative stress and preserving myocardial tissue and function.	(22)

Clinical Potential of Nicotinamide

Nicotinamide is recognized as one of the safest drugs in clinical practice. It should not be confused with nicotinic acid (also known as niacin, vitamin B3, and vitamin PP), which is also a vitamin B3 form, but exhibits more pharmacological and adverse effects than nicotinamide (23). It is well established that niacin (nicotinic acid) increases levels of HDL cholesterol, which has been suggested to decrease the risk of cardiovascular events. However, in a trial, AIM-HIGH, a slow-release form of niacin used for its effect on lipids, was found not to affect cardiovascular events. In addition to that, the trial was halted prematurely on evidence that niacin and statins combined increased stroke risk in this group (24). It is important to point out that, in contrast to nicotinic acid, nicotinamide has no lipid and vascular effects, it is not a compound used in the AIM-HIGH trial, and no similar effect of nicotinamide would be expected (23).

Current therapeutic use of nicotinamide is confined to the treatment of acne vulgaris, diabetes mellitus, and head and neck cancer, all of which are in doses above 500 mg/day (25-27), much higher than recommended dietary intakes of niacin equivalents, which are 14-16 mg daily (28). It has been suggested that chronic intake of nicotinamide below 3000 mg/day is safe and virtually devoid of adverse effects (29). The maximal effective cardioprotective dose in mice was the dose that is equivalent to 500 mg/day of nicotinamide in people (14, 30; Figure 1), which suggests that the use of nicotinamide for cardioprotection is likely to be safe and without many adverse effects.

Toxicology and pharmacokinetic properties of nicotinamide are well established (31). Although nicotinamide has been used in high doses to treat patients suffering from inflammatory skin disease, diabetes mellites and cancers (32-36), no major regulatory bodies have officially approved nicotinamide for the treatment of these diseases. The European Food Safety Authority (EFSA) has established the tolerable upper intake level (UL) for nicotinamide to prevent potential adverse effects, and that is 900 mg

per day (37). Tablets and capsules containing nicotinamide on its own in a range of doses (50-500 mg) are readily available over the counter and can be easily purchased/bought from multiple sources, including Amazon and eBay (38, 39).

The whole body of research up to date strongly suggests that nicotinamide possesses cardioprotective properties while being safe. As such, it could be a safe and efficient therapeutic against a range of cardiac and non-cardiac conditions where increased cardiac resistance to metabolic stress is beneficial. However, the fact is that no clinical studies have been done so far to test nicotinamide as a cardioprotective agent. Therefore, randomized controlled clinical trials are needed to examine nicotinamide's possible role in clinical practice, define optimal dosing strategies, and understand its long-term effects. Having said that, nicotinamide, as an already well-tested compound for other indications, could be quickly introduced in clinical practice for cardioprotection.

Conclusion

Nicotinamide possesses cardioprotective properties, but this is yet to be tested on humans. However, taking into consideration the fact that nicotinamide is a well-tested compound in humans with well-established safety, it is logical to expect that clinical trials would yield positive results, and that nicotinamide could be quickly introduced into clinical practice as a cardioprotective agent.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

QD wrote, reviewed, and edited the original draft.

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Nikotinamid: Kardioprotektivni oblik vitamina B3

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Kratak sadržaj

Nikotinamid, oblik vitamina B3, zapažen je kao potencijalni kardioprotektivni agens kod ishemijsko-reperfuzijske (I/R) povrede, koja je ključni faktor u patogenezi infarkta miokarda, srčane insuficijencije i drugih kardiovaskularnih bolesti. Ovo jedinjenje igra značajnu ulogu u energetskom metabolizmu, popravci DNK i preživljavanju ćelija tako što učestvuje u biosintezi NAD+, koenzima esencijalnog za redoks reakcije.

U osnovi kardioprotekcije koju pruža nikotinamid leži mehanizam koji uključuje pojačanu biosintezu NAD+, koja zatim reguliše SUR2A kako bi se modulisali ATP-senzitivni K+ (KATP) kanali, utiče na aktivnost sirtuina i deluje na aktivnost poli(ADP-riboza) polimeraza (PARP) kako bi se očuvali nivoi NAD+. Pored toga, nikotinamid ispoljava antiinflamatorna svojstva, reguliše autofagiju i deluje antioksidativno, što zajedno doprinosi njegovom potencijalu da ublaži uticaj I/R povrede na miokard.

Uprkos širokom spektru terapijskih primena i sigurnom profilu, od ključnog je značaja imati na umu razlike između nikotinamida i druge forme vitamina B3, nikotinske kiseline (niacina), posebno u pogledu njihovih efekata na lipidni status i vaskularne funkcije. Za razliku od niacina, nikotinamid ne utiče na nivoe lipida niti povećava rizik od kardiovaskularnih događaja, što naglašava njegovu sigurnost za kliničku upotrebu u preporučenim dozama. Ipak, do sada nije sprovedena nijedna klinička studija o nikotinamidu u kontekstu kardioprotekcije. Jasno je da su potrebna randomizovana kontrolisana ispitivanja kako bi se ispitala moguća uloga nikotinamida u kliničkoj praksi, definisale optimalne strategije doziranja i razumeli njegovi dugoročni efekti. Međutim, s obzirom na istoriju upotrebe nikotinamida, ovo je jedinjenje koje bi moglo brzo biti uvedeno u kliničku praksu za kardioprotekciju.

Ključne reči: kardioprotekcija, nikotinamid